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L24: Entry 191 of 238 File: USPT Nov 7, 1995

DOCUMENT-IDENTIFIER: US 5464823 A
** See image for Certificate of Correction **
TITLE: Mammalian antibiotic peptides

Detailed Description Text (69):
Antibodies to the protegrins of the invention may also be produced using standard immunological techniques for production of polyclonal antisera and, if desired, immortalizing the antibody-producing cells of the immunized host for sources of monoclonal antibody production. Techniques for producing antibodies to any substance of interest are well known. It may be necessary to enhance the immunogenicity of the substance, particularly as here, where the material is only a short peptide, by coupling the hapten to a carrier. Suitable carriers for this purpose include substances which do not themselves produce an immune response in the mammal to be administered the hapten-carrier conjugate. Common carriers used include keyhole limpet hemocyanin (KLH), diphtheria toxoid, serum albumin, and the viral coat protein of rotavirus, VP6. Coupling of the hapten to the carrier is effected by standard techniques such as contacting the carrier with the peptide in the presence of a dehydrating agent such as dicyclohexylcarbodiimide or through the use of linkers such as those available through Pierce Chemical Company, Chicago, Ill.

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L24: Entry 227 of 238 File: USPT Dec 15, 1987

DOCUMENT-IDENTIFIER: US 4713366 A
** See image for Certificate of Correction **
TITLE: Antigenic modification of polypeptides

Detailed Description Text (132):
Additional modifying groups for modifying whole hormones or their subunits are those groups obtained by reaction of the polypeptides with dinitrophenol, trinitrophenol, and S-acetomercaptosuccinic anhydride, while suited for utilization as carrier-modifiers in conjunction with fragments, are polytyrosine in either straight or branched chains, polyalanines in straight or branched chains, biodegradable polydextrane, e.g. polymerized sugars such as sucrose copolymerized with epichlorohydrin, e.g. Ficoll 70 and Ficoll 400 (a synthetic copolymer of sucrose and epichlorohydrin having an average molecular weight of 400,000.+-.100,000 intrinsic viscosity of 0.17 dl/g. specific rotation [alpha].sup.20.sub.D of +56.5.degree., available from Pharmacia Fine Chemicals, Pharmacia Laboratores, Inc. 800 Centennial Ave., Piscataway, NJ 08854) or a polyglucose such as Dextran T 70 (a glucan containing alpha-1,6-glucosidic bonds and having an average molecular weight of approximately 70,000, synthesized microbiologically by the action of Leuconostoc mesenteroides strain NRRL B-512 on sucrose), serum proteins such as homologous serum albumin, hemocyanin from Keyhole limpet (a marine gastropod mollusk) viruses such as influenza virus (type A, B, or C) or poliomyelitis virus, live or killed, Types 1, 2 and 3 of tetanus toxoid, diphtheria toxoid, cholera toxoid or somewhat less preferably, natural proteins such a thyroglobulin, and the like. Generally, synthetic modifiers are preferred over the natural modifiers. However, carrier-modifiers found particularly suitable for conjugation with the above-discussed fragment structures are flagellin, tetanus toxoid and an influenza subunit, for example, the preparation of which is described by Bachmeyer, Schmidt and Liehi, "Preparation and Properties of a Novel Influenza Subunit Vaccine", Post-Graduate Medical Journal (June, 1976), 52,360-367. This influenza subunit was developed as a vaccine which incorporates essentially only the two viral proteins, haemagglutinin and neuraminidase. Containing substantially only these two essential immunogens, the subunit represents a preparation which does not contain other protein and lipid antigens which may be found to cause underdesired side reactions. A secondary benefit may be realized through the utilization for example, of the influenza subunit, poliomyelitis virus, tetanus toxoid, diphtheria toxoid, cholera toxoid or the like as a modifier-carrier, inasmuch as beneficial antibodies will be raised to that modifier-carrier as well as the hormonal fragment conjugated thereto

Detailed Description Text (176):
There is a further, although usually minor, disadvantage which is shared by both the bi-functional organic reagent polymerization technique and the conjugation technique, namely the introduction of exogenous materials into the body of the animal being treated. The bi-functional organic reagent technique introduces a relatively small proportion of exogenous material into the animal being treated (and even this relatively small proportion of non-endogenous material can be chosen so that it is not strongly immunogenic), while the conjugation technique tends to introduce a much higher proportion of non-endogenous material and will usually provoke the formation of substantial quantities of antibodies to the carrier as well as to the polypeptide. Although, as mentioned above, the formation of antibodies to the carrier (and in some cases to the bi-functional organic reagent used for coupling either in the conjugation or polymerization techniques) may sometimes be useful (for example, a vaccine based upon an HCG peptide coupled to diphtheria toxoid and intended for fertility control has the incidental advantage of also confering protection against diphtheria), there are some occasions on which it may not be desirable to provoke the formation of relatively large quantities of antibodies to the carrier; for example if one wishes to use a vaccine containing a modified polypeptide of the invention to treat a patient with a

carcinoma or a serious viral infection, it may be desirable to avoid overstraining the patient's immune system by challenging it not only with the modified polypeptide to which antibodies are desired, but also with the carrier.

Detailed Description Text (417):
The results obtained in rabbits are shown in Table 13 below. The highest antibody levels were obtained in the rabbits immunized with conjugates of bovine gamma globulin, tetanus toxoid and diphtheria toxoid, there being no significant difference between the peak antigen titers of these three carriers. Significantly lower antibody levels were found in rabbits immunized with bacterial carriers, while synthetic polypeptide and sugar carriers produced antibody levels which were significantly lower than those of bacterial carriers.

Detailed Description Text (421):
Moreover the results presented above strongly suggest that the best carriers for use in humans or other primates are tetanus toxoid and diphtheria toxoid. While the antibody levels in rabbits for bovine gamma globulin, tetanus toxoid and diphtheria toxoid are not significantly different, the antibody levels produces in mice with conjugates of the bovine gamma globulin are not as high as those produced by conjugates of the two toxoids. Immunization of humans or other primates with tetanus and diphtheria toxoids is acceptable and even advantageous (since a single vaccination can then provide protection against tetanus or diphtheria as well as an isoimmunogenic action), whereas injections of non-primate gamma globulins may not prove safe. Conjugates of either tetanus toxoid or diphtheria toxoid with a peptide:carrier ration of 20-30 peptides per 10.sup.5 daltons of carrier evoked large titers of antibody reactive to HCG and would therefore appear to be suitable for an anti-HCG vaccine.

CLAIMS:

15. A modified polypeptide for isoimmunologically controlling biological action in a mammal by antibody formation, the modified polypeptide comprising a peptide having an amino acid sequence in its unmodified form of: ##STR9## or a sequence substantially immunologically equivalent to one of these sequences, said peptide having the two cysteine residues corresponding to the cysteine residues at positions 38 and 57 of the beta-subunit of human chorionic gonadotropin having their sulfur atoms linked in a disulfide bridge, said peptide having been chemically modified outside the body of said mammal by coupling said peptide to a carrier selected from the group consisting of a diazosulfanilic acid, dinitrophenol, trinitrophenol, S-acetomercaptosuccinic anhydride, (poly)tyrosine, (poly)alanine, poly(lysine), (poly)dextran, thyroglobulin, natural proteins, polymerized sugars, serum protein, diphtheria toxoid and tetanus toxoid, said peptide having the properties of:

(a) in unmodified form, being non-immunogenic to said mammal and having a molecular structure similar to a fragment of an endogenous protein hormone, the biological function of which it is desired to inhibit, and

(b) in modified form, causing antibodies to be formed in the body of the mammal which inhibit the biological function of said endogenous protein hormone following administration of the modified form into the body of said mammal.

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L28: Entry 2 of 2 File: USPT Sep 4, 2001

DOCUMENT-IDENTIFIER: US 6284533 B1
TITLE: Plasmid-based vaccine for treating atherosclerosis

Brief Summary Text (25):
The immunogenic fusion polypeptide encoded on a plasmid as described herein comprises a T cell epitope portion and a B cell epitope portion. A T cell epitope portion encoded on the plasmid of this invention comprises a non-endogenous CETP protein, or fragment thereof, that contains a broad range or "universal" helper T cell epitope which binds the antigen presenting site of multiple (i.e., 2, 3, 4, 5, 6 or more) class II major histocompatibility (MHC) molecules and can form a tertiary complex with a T cell antigen receptor, i.e., MHC:antigen:T cell antigen receptor. By "non-endogenous CETP protein" is meant a protein which is not the endogenous CETP of the individual who is to be administered a plasmid of this invention. Such non-endogenous CETP proteins, or fragments thereof, useful as T cell epitope portions of the immunogenic fusion polypeptide encoded by plasmids of this invention include tetanus toxoid (particularly peptides of tetanus toxoid having amino acid sequences of amino acids 2-15 of SEQ ID NO:7 and amino acid sequence of SEQ ID NO:10); diphtheria toxin (particularly peptides having amino acid sequences of amino acids 271-290, 321-340, 331-350, 351-370, 411-430, and 431-450 of SEQ ID NO:9); class II MHC-associated invariant chain; influenza hemagglutinin T cell epitope; keyhole limpet hemocyanin (KLH); a protein from known vaccines including pertussis vaccine, the Bacile Calmette-Guerin (BCG) tuberculosis vaccine, polio vaccine, measles vaccine, mumps vaccine, rubella vaccine, and purified protein derivative (PPD) of tuberculin; and also synthetic peptides which bind the antigen presenting site of multiple class II histocompatibility molecules, such as those containing natural amino acids described by Alexander et al. (Immunity, 1: 751-761 (1994)). When attached to a CETP B cell epitope portion, the T cell epitope portion enables the immunogenic fusion polypeptide to break tolerance in order for antibodies to be made that react with endogenous CETP. By "breaking tolerance" is meant forcing an organism to mount an immune response to a protein, such as endogenous CETP, that the organism does not normally find immunogenic

Detailed Description Text (9):
Broad range antigenic helper T cell epitopes are known in the art. These include, for example, epitopes of tetanus toxoid (TT) and diphtheria toxoid (DT) (see, for example, Panina-Bordignon, P., et al., Eur. J. Immunol., 19: 2237-2242 (1989) (characterization of universal tetanus toxoid helper T cell epitope peptides); Etlinger, H., Immunol. Today, 13: 52-55 (1992); Valmori, D., et al., J. Immunol., 149: 717-721 (1992) (use of universal TT epitopes in candidate anti-malarial vaccine); Raju et al., Eur. J. Immunol., 28: 3207-3214 (1995) (broad range T cell epitopes of DT); Talwar, G. P., et al., Proc. Natl. Acad. Sci. USA, 91: 8532-8536 (1994) (use of TT and DT as universal epitopes in anti-human chorionic gonadotropin vaccine); Talwar, G. P., et al., Proc. Natl. Acad Sci. USA, 91: 9532-8536 (1994)).

Detailed Description Text (11):
Plasmids of this invention may encode a variety of non-endogenous CETP proteins, or fragments thereof, such as tetanus toxoid, particularly peptides of tetanus toxoid having amino acid sequences of amino acids 2-15 of SEQ ID NO:7 (a corresponding nucleotide coding sequence is nucleotides 13-54 of SEQ ID NO:9) and amino acid sequence of SEQ ID NO 10. Another source of universal or broad range T cell epitopes useful in the plasmids of this invention is diphtheria toxin, particularly peptides having amino acid sequences of amino acids 271-290, 321-340, 331-350, 351-370, 411-430, and 431-450 of SEQ ID NO 9. An example of corresponding nucleotide sequences encoding these broad range T cell epitopes from diphtheria toxin are nucleotides 811-870, 961-1020, 991-1050, 1051-1110, 1231-1290, and 1291-1350 of SEQ ID NO 8, respectively. Other sources of universal or broad range T cell epitopes that may be encoded on plasmids of

this invention include, but are not limited to, class II MHC-associated invariant chain; hemagglutinin; keyhole limpet hemocyanin (KLH); a protein from known vaccines including pertussis vaccine, the Bacile Calmette-Guerin (BCG) tuberculosis vaccine, polio vaccine, measles vaccine, mumps vaccine, rubella vaccine, and purified protein derivative (PPD) of tuberculin; and also synthetic peptides as described by Alexander et al. (1994).

Detailed Description Text (63):
The results of the above experiment using a rabbit model for atherosclerosis indicate that the plasmid-based vaccines of this invention may be used to prevent or treat atherosclerosis in other vertebrates. By analogy to the treatment for inhibiting atherosclerosis in rabbits illustrated in Example III, similar plasmid constructs may be made for other vertebrates, including humans. Such plasmids encode an immunogenic fusion polypeptide comprising a universal or broad range T cell epitope, such as from tetanus toxoid or diphtheria toxoid, linked in the same reading frame to at least one, more preferably two, B cell epitopes of the endogenous CETP of the individual. An example of a plasmid-based vaccine for endogenous human CETP contains a DNA sequence encoding a translation initiating methionine linked to a TT polypeptide, such as in nucleotides 10-54 of SEQ ID NO:5, which is linked in the same reading frame (with or without intervening linker sequences) to a DNA sequence encoding regions of human CETP analogous to those used in the rabbit CETP plasmid-based vaccine, such as nucleotides 1045-1101 and 1381-1428 of SEQ ID NO:3 encoding amino acids 349-367 and 461-476 of SEQ ID NO:4, respectively. Preferably, the DNA sequence in the plasmid for use as a vaccine against human endogenous CETP also includes regions as shown in FIG. 5, such as translational start and stop codons and flanking restriction endonuclease sites that are commonly employed for plasmid construction and gene expression.

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L28: Entry 1 of 2 File: USPT Jun 25, 2002

DOCUMENT-IDENTIFIER: US 6410022 B1
TITLE: Modulation of cholesteryl ester transfer protein (CETP) activity

CLAIMS:

9. The vaccine composition according to claim 7 wherein the T cell epitope portion of the antigenic vaccine hybrid peptide is a universal helper T cell epitope selected from the group consisting of T cell epitope amino acid sequences of tetanus toxoid, diphtheria toxoid, pertussis vaccine, Bacile Calmette-Guerin (BCG), polio vaccine, measles vaccine, mumps vaccine, rubella vaccine, purified protein derivative of tuberculin, keyhole limpet hemocyanin, and combinations thereof.

17. The method according to claim 16, wherein the helper T cell epitope portion is selected from the group consisting of universal helper T cell epitope amino acid sequences of tetanus toxoid, diphtheria toxoid, pertussis vaccine, Bacile Calmette-Guerin (BCG), polio vaccine, measles vaccine, mumps vaccine, rubella vaccine, purified protein derivative of tuberculin, keyhole limpet hemocyanin, and combinations thereof.